Stability of development and behavior of preterm children

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CHAPTER 3

Stability of developmental problems after school entry of moderately-late preterm and early preterm-born children

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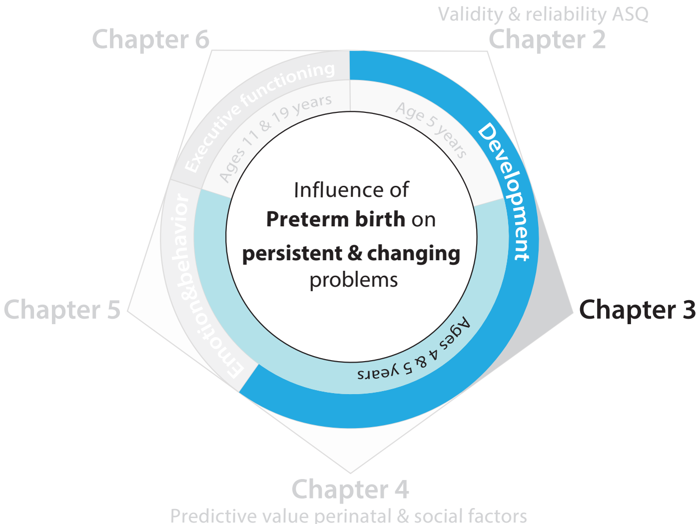


CHAPTER 3 | **Stability of developmental problems of moderately-and-late preterm and early preterm children after school entry**

ABSTRACT

Objective To assess the stability of developmental problems in moderately-and-late-preterm children (MLPs) compared with early-preterm children (EPs) and fullterm children (FTs), before school entry at age 4, and one year after school entry at age 5.

Study Design We included 376 EPs, 688 MLPs, and 403 FTs from the LOLLIPOP cohort-study. Developmental problems were assessed by the total score and the 5 domain scores of the Ages and Stages Questionnaire at ages 4 (ASQ-4) and 5 (ASQ-5). From the combinations of normal and abnormal ASQ-4 and ASQ-5 scores we constructed four categories: consistently normal, emerging, resolving, and persistent problems.

Results The ASQ-4 total score was abnormal more frequently in MLPs (7.9%, P=.016) and EPs (13.0%, P<.001) compared with FTs (4.1%). Compared with the ASQ-5 total score, MLPs had persistence and change comparable to FTs, and EPs had significantly higher rates than FTs of persistent (8.4% versus 2.2%, P<.001) and emerging problems (7.8% versus 2.7% P=.001). On the underlying domains, both EPs and MLPs had mainly emerging motor problems and resolving communication problems, but the changing rates of MLPs were lower.

Conclusions After school entry, the overall development of MLPs had stability patterns comparable with FTs, whereas EPs had higher rates of persistent and emerging problems. On the underlying domains, MLPs had patterns comparable with EPs, but at lower rates.

INTRODUCTION

Preterm birth (<36 weeks' gestational age (GA)) has important consequences for further short-term and long-term development. Worldwide, 11% of children are born preterm.[1] At preschool age, 15-24% of early-preterm children (EPs, <32 weeks GA) and 8-25% of moderately-and-late-preterm children (MLPs, 32-35 weeks GA) have developmental problems, in comparison with 4-14% of fullterm children (FTs).[2,3] After school entry, similar prevalence rates of developmental problems are reported among preterm children.[4,5] However, the preterm children with developmental problems at preschool age may not be the same children as those with developmental problems at early school age, as school entry stimulates development but also puts more demands on children's abilities.

Evidence on the stability of developmental problems of preterm children mainly concerns EPs and/or children with a low birth weight (<1500g).[6,7] These EPs show, at age 4, higher rates of developmental problems on all domains,[8] which both emerge and resolve after school entry.[9–11] However, the evidence per developmental domain is inconsistent.[6,12] MLPs have at age 4, problems with communication, fine motor function, and personal social skills.[8] After school entry, these preschool developmental problems of MLPs were no good predictors for school problems and school readiness (predictive values 10.4-17.1%).[13,14] However, to our knowledge no studies assessed the association of developmental problems among MLPs before and after school entry.

The aim of this study is to assess the stability patterns of developmental problems, overall and per domain, among MLPs compared with EPs and FTs, between the time before school entry and one year after school entry. We expected that developmental problems may both emerge and resolve after school entry, as this puts higher demands on their abilities but also provides more opportunities to practice these abilities by stimulating activities and by interacting with other children. In addition, we expected that problems might emerge more frequently in EPs and resolve more frequently in MLPs, because MLPs may have a less disrupted white matter maturation and more cortical plasticity than EPs.[15,16] This may help to determine in advance of school entry which preterm children are likely to have the highest risks of persistent and emerging problems after school entry, and in which specific developmental domains. Such insight is important for the prevention and early identification of developmental problems in well-child care and neonatal follow-up, because early identification of children at risk of developmental problems could facilitate early intervention, increasing the likelihood of normal development.

METHODS

Study design and participants

This study was part of the LOLLIPOP cohort study, which has its main focus on the growth and development of MLPs, compared with both EPs and FTs. The LOLLIPOP cohort is a community-based sample of EPs and MLPs and a random sample of FTs born in 2002 and

2003 in the Netherlands. This community-based sample came from 13 preventive child health centers. These centers monitored a sample representative of 25% of the children born in 2002 and 2003 in the Netherlands. Children were included before their regular well-child visit at the age of 43-49 months. All children born before 36 weeks GA without major congenital malformations, congenital infections, or syndromes were sampled. After each second preterm child sampled, the next FT child (38-41 weeks GA), without the aforementioned exclusion criteria, was drawn from the same files to serve as a control. In addition, the EP sample was enriched with a sample of EPs born in 2003, taken from five of the ten neonatal intensive care units in the Netherlands. A detailed description of this study cohort can be found elsewhere.[8]

Measures

Developmental problems: Ages and Stages Questionnaire (ASQ)

Developmental problems were measured with the Ages and Stages Questionnaire (ASQ), which is, worldwide, the most commonly used parent-completed developmental screener.[17] We used the validated Dutch versions appropriate for ages 4 (ASQ-4) and 5 years (ASQ-5).[18–20] The ASQ contains five domains: communication, gross motor, fine motor, problem solving, and personal-social skills. Each domain is assessed using six questions about reaching milestones. The response format is 'yes' (10 points), 'sometimes' (5 points), or 'not yet' (0 points). The scores of the questions were summed into a score for each domain separately, and overall: the ASQ total score. Subsequently, these scores were categorized into normal and abnormal scores, defined as abnormal if the score was more than 2 standard deviations below the mean of the Dutch reference population.[19,20]

We combined the dichotomous ASQ-4 and ASQ-5 outcomes on the five ASQ domains and the ASQ total score to form four stability categories for each ASQ outcome: stable normal, emerging problems, resolving problems, and persistent problems. The stable normal group had normal scores at both ages, the emerging problems group had a normal ASQ-4 score and an abnormal ASQ-5 score, the resolving problems group had an abnormal ASQ-4 and a normal ASQ-5, and the persistent problems group had two abnormal scores.

Gestational age

The preterm group was split into an EP category (25-31 weeks GA) and an MLP category (32-35 weeks GA). GA was determined in completed weeks, and was based on early ultrasound measurements in >95% of the cases. For the remaining cases, only clinical estimates based on last menstrual date were available; these were checked against clinical estimates of gestational age after birth.

Covariates

Covariates were selected based on previous studies of developmental problems in preterm children,6,7,21,22 and were divided into perinatal characteristics and family characteristics. Perinatal characteristics included gender, small for GA, and being part of a multiple pregnancy. Small for GA was determined as a birth weight below the 10th centile of the Dutch growth chart.23 Family characteristics included low education of both mother and father, ethnicity (birth of parent and/or child outside the Netherlands), and single-parent family. Low education was defined as maximally primary education, or low-level technical or vocational training.

Procedure

One month before the children's well-child visit at age 43-49 months, parents received information about the LOLLIPOP study, an informed consent form, the ASQ-4, and a questionnaire about family and perinatal characteristics. These were returned by the parents at their child's scheduled well-child visit. Following parental informed consent, we retrospectively recorded perinatal characteristics from discharge letters of mother and child, well-child care records, and information from linked national birth registers. Approximately 4-6 weeks before the child's fifth birthday, parents received the ASQ-5. The ASQ-5 was returned by mail.

The ASQ-4 and ASQ-5 were completed within the determined time windows19,20 (43-49 months and 57-63 months after birth, respectively) for 1467 children, including 376 EPs, 688 MLPs, and 403 FTs (Figure 1). The children with only an ASQ-4 (within the time window) but not an ASQ-5 (no ASQ-5 n= 484, outside time window n=25) had more frequently an abnormal ASQ-4 total score than the children with completed ASQ's at both ages (11.1% versus 8.1%, P=.048), and their parents had more frequently a low education (28.6% versus 14.2% P<.001). Similar rates of preterm children and FTs were lost to follow-up (25.8% versus 25.8%, P=.988).

Analyses

First, we compared characteristics between the GA groups (EPs, MLPs and FTs). Second, we determined the overall stability per GA group, by comparing rates of abnormal scores on the ASQ-4 and ASQ-5. Third, we assessed individual stability within the GA groups in two ways: by calculating the predictive values, and by comparing prevalence rates of the four stability categories (consistently normal, resolving problems, emerging problems, persistent problems). The 'predictive value of a normal ASQ-4' was defined as the proportion of children with a normal ASQ-5 out of the children with a normal ASQ-4, and the 'predictive value of an abnormal ASQ-4' was defined as the proportion of children with an abnormal ASQ-5 out of the children with an abnormal ASQ-4. We performed the analyses on the four stability categories both crude, and adjusted for perinatal and family characteristics (gender, small-for-gestational age, being part of a multiple birth, low education level of the parents, non-Dutch birth country of parent or children, and single-parent family). All tests performed were 2-tailed and considered as significant when P<.05.

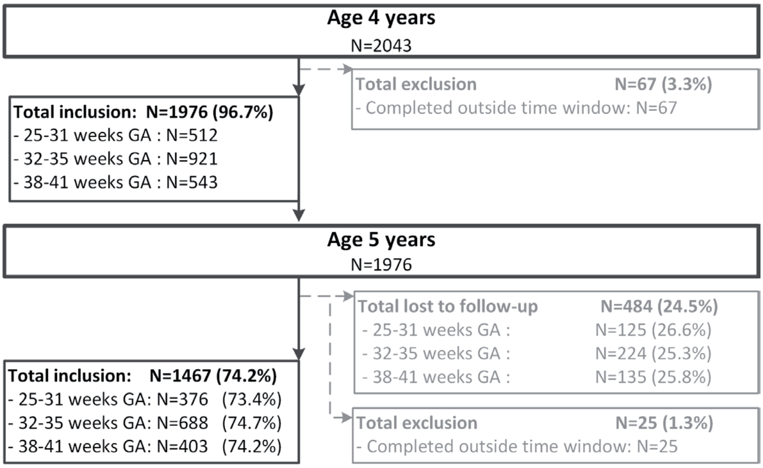


Figure 1: Overview of the children which were included in this study.

RESULTS

Table 1 shows the main characteristics of the EPs, MLPs and FTs. The EPs and MLPs differed significantly from the FTs in characteristics associated with prematurity (small for GA PEP<.001, being twin PEP and PMLP<.001, male sex PMLP<.001) and family composition (single-parent family PEP=.011 PMLP=.002, education level of parents PMLP=.012, birth country of parents PEP=.013).

Stability of developmental problems per GA group

Table 2 shows the rates of abnormal scores on the ASQ-4 and ASQ-5 per GA category. The total ASQ-4 score was abnormal more frequently in EPs (13.0%, P<.001) and MLPs (7.9%, P=.004), compared with FTs (4.1%) (Table 2). However, the total ASQ-5 score was abnormal more frequently only in EPs (16.2%, P<.001) and not in MLPs (7.3%, P=.121), compared with FTs (4.8%) (Table 2). Concerning the ASQ domains, EPs had significantly more abnormal scores on all ASQ domains at both ages 4 and 5 than did FTs (P's≤.004), except for communication on the ASQ-5 (P=.067). MLPs had significantly more abnormal scores than FTs on different domains on the ASQ-4 (communication P=.013, fine motor P=.004, and personal social P=.005) than on the ASQ-5 (gross motor P<.001 and personal social P=.003), in which rates of abnormal communication scores were lower on the ASQ-5 than the ASQ-4 (3.9% P=.349 versus 10.0% P=.013, respectively), but rates were higher on the ASQ-5 than on the ASQ-4 regarding abnormal gross motor scores (10.2% P<.001, versus 5.1% P=.292, respectively) and abnormal fine motor scores (10.0% P=.105 versus 8.0% P=.004, respectively).

***Table 1**: Characteristics of children by gestational age (GA) category*

	FT n=403 n(%)	**MLP** n=688 n(%)	**EP** n=376 n(%)
GA *median(25-75th percentile)*	40 (39-40)	34 (33-35)***	30 (28-31)***
Boy	190 (47.1)	401 (58.3)***	191 (50.8)
Small for GA	28 (6.9)	64 (9.3)	81 (21.5)***
Twin	5 (1.2)	178 (25.9)***	113 (30.1)***
Single parent family	8 (2.0)	44 (6.4)**	21 (5.6)*
Low educational level - of both parents	43 (10.8)	111 (16.4)*	51 (13.7)
- of mother	88 (21.9)	181 (26.5)	84 (22.4)
- of father	101 (25.6)	210 (31.1)*	98 (26.4)
Non-Dutch birth country of parent and/or child	17 (4.3)	49 (7.2)	32 (8.7)*

** P<.05; **P<.01; ***P<.001 with crude logistic regression analyses FT as reference.*
FT=fullterm; MLP=moderately-and-late preterm; EP=early preterm;

Stability of developmental problems within the GA groups

Table 2 also shows the individual persistence and change of developmental problems as measured by the predictive values of normal and abnormal ASQ-4 scores for the corresponding ASQ-5 scores. Regarding total scores of both preterm groups and FTs, the predictive values of a normal ASQ-4 were higher than the predictive values of an abnormal ASQ-4 (91-97% and 50-63%, respectively). The predictive value of a normal ASQ-4 was lowest for EPs (91% versus 97% for FTs, P=.001).

Figure 2 shows an overview of the individual persistence and change between the ASQ-4 and ASQ-5 for the four stability categories. The majority of the EPs, MLPs and FTs had consistently normal ASQ total scores (78.9%, 88.8% and 92.9%, respectively). Compared to FTs, EPs had significantly more persistent (8.4% versus 2.2%, P<.001), emerging (7.8% versus 2.7%, P=.001), and resolving problems (4.9% versus 2.2%, P=.026) on the ASQ total score and on most ASQ domain scores. The stability of the ASQ total score of MLPs was comparable with that of FTs (P≥.080). However, on the underlying domains stability patterns differed between MLPs and FTs. Rates of MLPs in the stability categories were in between EPs and FTs for the domains communication (Ppersistent=.036), gross motor (Pemerging=.001), fine motor (Presolving=.034), and personal social (Pemerging=.015 Presolving=.020), but very comparable with FTs for problem solving (P≥.140) and the total score (P≥.080). Regarding both EPs and MLPs, communication problems mainly resolved (11.2% P=.003, 7.5% P=.150, respectively versus 5.2%), and motor problems emerged (gross motor: 10.2% P<.001, 7.1%

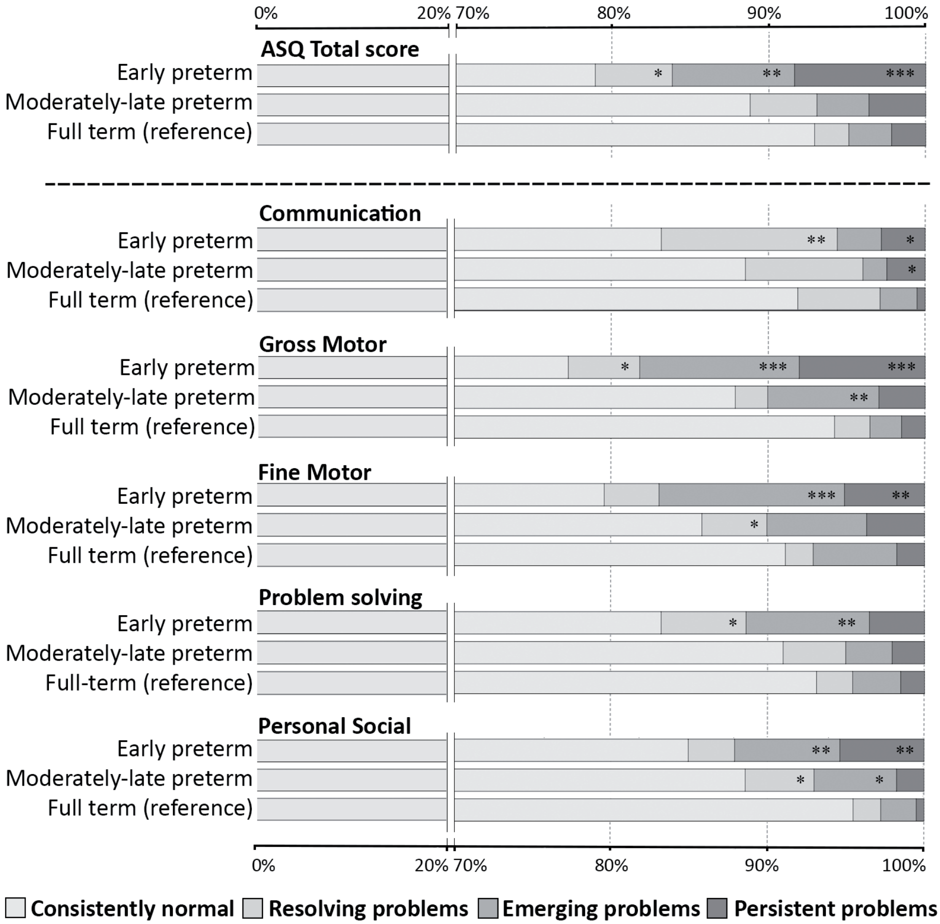
***Table 2**: Rates of abnormal ASQ scores, and predictive values (PV) of normal and abnormal ASQ-4 total and domain scores, for the corresponding ASQ-5 scores, per gestational age category.*

	Fullterm	Moderately-and-late preterm	Early preterm
Overall scores			
Total score			
Abnormal on ASQ-4 n(%)	16 (4.1)	**53 (7.9)***	**48 (13.0)*****
Abnormal on ASQ-5 n(%)	18 (4.8)	47 (7.3)	**57 (16.2)*****
PV normal ASQ-4	0.97	0.96	**0.91****
PV abnormal ASQ-4	0.50	0.46	0.63
Scores per domain			
Communication			
Abnormal on ASQ-4 n(%)	22 (5.5)	**68 (10.0)***	**50 (13.4)*****
Abnormal on ASQ-5 n(%)	11 (2.8)	26 (3.9)	20 (5.6)
PV normal ASQ-4	0.98	0.98	0.97
PV abnormal ASQ-4	0.09	0.25	0.20
Gross motor			
Abnormal on ASQ-4 n(%)	15 (3.7)	35 (5.1)	**47 (12.5)*****
Abnormal on ASQ-5 n(%)	14 (3.5)	**70 (10.2)*****	**68 (18.1)*****
PV normal ASQ-4	0.98	**0.93****	**0.88*****
PV abnormal ASQ-4	0.40	0.59	0.64
Fine motor			
Abnormal on ASQ-4 n(%)	14 (3.5)	**55 (8.0)****	**32 (8.5)****
Abnormal on ASQ-5 n(%)	28 (7.1)	68 (10.0)	**63 (16.9)*****
PV normal ASQ-4	0.94	0.93	**0.87****
PV abnormal ASQ-4	0.50	0.47	0.59
Problems solving			
Abnormal on ASQ-4 n(%)	15 (3.8)	41 (6.0)	**34 (9.1)****
Abnormal on ASQ-5 n(%)	18 (4.5)	34 (5.0)	**42 (11.3)****
PV normal ASQ-4	0.97	0.97	**0.91****
PV abnormal ASQ-4	0.40	0.34	0.39
Personal social			
Abnormal on ASQ-4 n(%)	9 (2.2)	**42 (6.1)****	**31 (8.3)*****
Abnormal on ASQ-5 n(%)	11 (2.8)	**49 (7.1)****	**45 (12.1)*****
PV normal ASQ-4	0.98	**0.94***	**0.93****
PV abnormal ASQ-4	0.22	0.29	**0.65***

** P<.05; **P<.01; ***P<.001 with crude logistic regression analyses with fullterm as reference. ASQ-4: ASQ score at age 4; ASQ-5: ASQ score at age 5*

P=.001, respectively versus 2.0%; fine motor: 11.8% *P*=.001, 6.4% *P*=.388, respectively versus 5.3%). After adjustment for confounders, EPs still were more likely to have persistent (OR(95%confidence interval)) 3.02 (1.28-7.10), P=.012) and emerging (OR(95%CI) 4.37 (1.87-10.20), P<.001) problems on the ASQ total score in comparison with FTs, but not significantly more resolving problems (OR(95%CI) 1.55(.061-3.94), P=.359).

Figure 2*: Rates of persistent and changing scores on the ASQ total score and the separate ASQ*



*domains between ages 4 and 5 years among early preterm, moderately-and-late preterm and fullterm children. * P<.05; **P<.01; ***P<.001, based on crude and adjusted multinomial logistic regression analyses with consistently normal FTs as reference category.*

DISCUSSION

This study demonstrated that in the period after school entry stability patterns of MLPs were comparable with those of FTs, whereas EPs had higher rates of persistent and emerging developmental problems than FTs had. With regard to the underlying domains, both MLPs and EPs showed more emerging motor problems and more resolving communication problems.

MLPs had stability rates comparable with FTs regarding their overall development and problem solving, but the stability rates of MLPs were in between the rates of EPs and FTs for the other developmental domains. These results indicate that the relation between the GA in weeks of prematurity and the stability of developmental problems varies by developmental domain. The stability patterns of total developmental problems and problem solving problems seem to be exponentially related to decreasing GA, with mainly the lowest GAs showing more persistent and changing problems. The stability patterns of the other underlying domains seem to be related linearly to decreasing GA, with persistent and changing problems gradually increasing with decreasing GA. These exponential and linear associations were also reported for developmental problems at a specific age.2,24–26 In summary, the degree of prematurity seems to have both exponential and linear relations with the stability patterns of developmental problems.

Both EPs and MLPs had higher rates of developmental problems than FTs before school entry, but one year after school entry only EPs had persistent and emerging problems more often. In a small cohort of preterm children 34-36 weeks GA, rates of developmental problems also decreased between ages 4, 8, and 18 months. Studies regarding EPs reported as predictive values for persistent (mild-severe) developmental problems: 50-71% for age 2/3 and age 5/8 years; we found a comparable value of 63%.9–11,27 MLPs may have more adaptation capacities than EPs, as MLPs are born at a higher GA and have fewer postnatal complications.24 Consequently, their brain's white matter maturation and cortical plasticity are less likely to be disrupted 15,16 This may result in MLPs having more abilities than EPs to improve their performance in a stimulating school environment.

Communication problems frequently resolved among both EPs and MLPs. We were surprised with these findings, as they contrast with studies among EPs <30 weeks GA at comparable ages.28,29 Howard et al. and Woods et al. found significant associations between communication problems and persistent language impairment from age 2/3 to age 5 years.28,29 In addition, 71% of the EPs from the study by Woods et al. had persistent language impairment between ages 3 and 5 compared with 20% in our EP group.28 Different perspectives may shed light on our contradictory findings. First, clinimetric issues may explain our findings: for example, the questions on communication in the ASQ-4 could be relatively more difficult than those in the ASQ-5. However, this is unlikely, given the high validity of the ASQ-4 and ASQ-5, and the high reliabilities of the scores for the domain communication (Cronbach's alphas 0.74 and 0.64, respectively).19,20 Second, school entry may enhance communication skills by the increased interaction with other children and the teacher, and activities as talking in group discussions, reading books, and singing songs. However, the children from the studies by Howard et al. and Woods et al. did not attend, or had only very recently attended school, as the age of school entry in Australia is 5 instead of 4 (as it is in the Netherlands). Therefore, unlike in our study, the stability of language skills of the children in these Australian studies could not be related to the event of school entry. Gross and fine motor problems frequently emerged and persisted among EPs and MLPs after school entry. Higher rates of persistent and emerging fine and gross motor problems were also reported previously in EPs ≤28 weeks GA between age 2/3 and age 5 years.6,30As with communication skills, we also expected school entry to have a positive influence because of stimulating activities like sporting during gymnastic lessons, playing outside and doing crafts. However, due to more demanding educational programs, schools allow less time for these motor activities. In addition, 5 year old children become less physically active than 3-4 year old children, and spend more time behind a screen.31 The combination of decreasing physical activity at home, and limited time for motor activities at school may explain the emerging and persistent motor problems of preterm children after school entry.

The strengths of this study are its large community based cohort, including EPs and MLPs as well as FTs. Furthermore, we used the same developmental screener at both ages. In addition, we were able to adjust our analyses for important confounders such as the educational level of the parents and being small-for-gestational age. Our study also has some limitations. First, we used the parent-reported ASQ, which might be less valid than a clinical assessment. However, testing in the (safe) home situation may be more representative for a child's performance than in a consultation room. Second, we had no information about interventions between ages 4 and 5 years which might have influenced persistence and change. Third, almost a quarter of the study sample was lost to follow-up between ages 4 and 5. This is probably due to the fact that at age 4 parents filled out the questionnaires in advance of a well-child visit, but at age 5 had to return it by mail. In addition, children lost to follow-up had more frequently a low ASQ-4 total score than those with both ASQ's. However, we do not expect that this loss to follow-up had a major influence on our findings as similar rates of preterm and FT children were lost to follow-up.

Our study showed that developmental problems among preterm children are not always persistent, but may emerge or resolve after school entry. Therefore, developmental surveillance of both EPs and MLPs should be continued at least until after school entry. Future research should determine if these trends continue during primary school ages among EPs and MLPs. Although we found different patterns for EPs, MLPs and FTs, the variation in individual persistence and change was also large within the GA categories. Therefore, future studies should determine the influence of other factors – such as physical activity, screen time, and educational programs – on the persistence and/or change of developmental problems of preterm children.

Conclusions

In conclusion, after school entry, in overall development the MLPs had stability patterns comparable with those of FTs, whereas EPs had higher rates of persistent and emerging problems. On most underlying domains, MLPs had, although with lower rates, stability patterns comparable with those of EPs: motor problems mainly emerged and communication problems resolved. Given the great differences in the stability of developmental problems of individual preterm children, developmental surveillance of these children should be continued after school entry.

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